Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

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Original Effective Date: 04/01/2008
Line(s) of Business: HMO; PPO
Current Effective Date: 05/27/2016
Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

Risk stratification of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) guides therapy decisions, which may include hematopoietic cell transplantation for those with poor risk features.

The evidence for allogeneic hematopoietic cell transplantation (allo-HCT) in individuals who have CLL/SLL and markers of poor-risk disease includes single-arm prospective and registry-based studies and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data suggests that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The evidence for autologous hematopoietic cell transplantation in patients who have CLL/SLL includes randomized controlled trials (RCTs), systematic reviews, and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup RCT suggests quality-of-life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach.

II. Policy

Allogeneic hematopoietic cell transplantation is covered (subject to Limitations and Administrative Guidelines) to treat chronic lymphocytic leukemia or small lymphocytic lymphoma in patients with markers of poor-risk disease (see Policy Guidelines). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.
III. Policy Guidelines

Staging and Prognosis of Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

Two scoring systems are used to determine stage and prognosis of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL). As outlined in Table 1, the Rai and Binet staging systems classify patients into 3 risk groups with different prognoses and are used to make therapeutic decisions.

Table 1: Rai and Binet Classification for CLL/SLL

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Risk</th>
<th>Description</th>
<th>Median Survival (yr)</th>
<th>Binet Stage</th>
<th>Description</th>
<th>Median Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis</td>
<td>&gt;10</td>
<td>A</td>
<td>3 or fewer lymphoid areas, normal hemoglobin and platelets</td>
<td>&gt;10</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate</td>
<td>Lymphocytosis + lymphadenopathy</td>
<td>7-9</td>
<td>B</td>
<td>3 or more lymphoid areas, normal hemoglobin and platelets</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>Lymphocytosis + splenomegaly + lymphadenopathy</td>
<td>7-9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Lymphocytosis+ anemia + lymphadenopathy or splenomegaly</td>
<td>1.5-5</td>
<td>C</td>
<td>Any number of lymphoid areas, anemia, thrombocytopenia</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>High</td>
<td>Lymphocytosis + thrombocytopenia + anemia, splenomegaly or lymphadenopathy</td>
<td>1.5-5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Because prognosis of patients varies within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table 2, according to availability in clinical centers.

Table 2: Markers of Poor Prognosis in CLL/SLL

<table>
<thead>
<tr>
<th>Community Center</th>
<th>Specialized Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Rai or Binet stage</td>
<td>IgVh wild type</td>
</tr>
<tr>
<td>Male sex</td>
<td>Expression of ZAP-70 protein</td>
</tr>
<tr>
<td>Atypical morphology or CLL/PLL</td>
<td>del 11q22-q23 (loss of ATM gene)</td>
</tr>
<tr>
<td>Peripheral lymphocyte doubling time &lt;12 mos</td>
<td>del 17p13 (loss of p53)</td>
</tr>
<tr>
<td>CD38⁺</td>
<td>Trisomy 12</td>
</tr>
</tbody>
</table>
Elevated beta2-microglobulin level  
Diffuse marrow histology  
Elevated serum lactate dehydrogenase level  
Fludarabine resistance  
Elevated serum CD23  
Elevated serum tumor necrosis factor-a  
Elevated serum thymidine kinase  

**Reduced-Intensity Conditioning for Allogeneic HCT**

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HCT. These include those patients whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allogeneic HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HCT if a complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, haploidentical donors—typically a parent or a child of the patient—with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens, have been under investigation as a stem-cell source. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

**IV. Limitations/Exclusions**

Autologous hematopoietic cell transplantation is not covered to treat chronic lymphocytic leukemia or small lymphocytic lymphoma as it is not known to be effective in improving health outcomes.

**V. Administrative Guidelines**

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>;thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>;specific cell depletion with harvest, T cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>;tumor cell depletion</td>
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### Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38212</td>
<td>;red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>;platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>;plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>;cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>;biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>;autologous transplantation</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic donor lymphocyte infusions</td>
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<tr>
<td>38243</td>
<td>;HPC boost</td>
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### ICD-10-PCS

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration, circulatory, transfusion, peripheral artery, open, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic)</td>
</tr>
<tr>
<td>Administration, circulatory, transfusion, peripheral artery, open, nonautologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic)</td>
</tr>
<tr>
<td>Administration, circulatory, transfusion, peripheral artery, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic)</td>
</tr>
<tr>
<td>Administration, circulatory, transfusion, peripheral artery, percutaneous, nonautologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic)</td>
</tr>
<tr>
<td>Extracorporeal Therapies, pheresis, circulatory, single, code by substance (cord blood, or stem cells, hematopoietic)</td>
</tr>
</tbody>
</table>
VI. Background

Conventional Preparative Conditioning for Hematopoietic Cell Transplantation

Hematopoietic stem-cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. The slower GVM effect is considered the potentially curative component, but it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during
which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma**

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in blood, bone marrow, lymph nodes, and spleen; in SLL they are generally confined to lymph nodes. The Revised European-American/WHO Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (eg, Richter transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and outcomes of treatment are comparable for the 2 diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses with median survivals of 6 to 10 years; however, the median survival of high-risk CLL or SLL may only be 2 years (see Policy Guidelines section). Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural history prompted investigation of hematopoietic stem-cell transplantation as a possible curative regimen.

**VII. Rationale**

**Literature Review**

This policy was created in 1999, and has been updated regularly based on literature searches of the MEDLINE and EMBASE online databases. The latest literature review was conducted through March 9, 2016. December 22, 2014.

The original Policy was based on 2 TEC Assessments. One from 1999 examined autologous hematopoietic stem-cell transplantation (autologous HCT) for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); the other from 2002 was on allogeneic hematopoietic stem-cell transplantation (allogeneic HCT) to treat CLL or SLL. Both documents indicated that existing data were insufficient to permit scientific conclusions regarding the use of either procedure, limited by interstudy heterogeneity in patient’s baseline characteristics, procedural differences, sample size, and short follow-up. A direct comparative analysis from the International Bone Marrow Transplant Registry (IBMTR) commissioned by TEC in 2002 to analyze allogeneic HCT results was insufficient to permit scientific conclusions on the net health outcome of this procedure for relapsed or refractory CLL or SLL.

Literature searches conducted between 2002 and July 2008 found no randomized trials of HCT compared with conventional-dose therapy for CLL or SLL. Recent reviews discuss uncertainties with respect to the
Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Type of transplant (autologous vs allogeneic), the intensity of pretransplant conditioning, the optimal timing of transplantation in the disease course, the baseline patient characteristics that best predict likelihood of clinical benefit from transplant, and the long-term risks of adverse outcomes. The conclusions reached in these reviews suggest that although autologous HCT may prolong survival in selected patients with CLL or SLL, for example, those with chemotherapy-sensitive malignancy who had a good response to front-line therapy and transplanted early in the course of disease, it has not yet been shown to be curative.

Allogeneic HCT

Allogeneic HCT has been under investigation for the past 2 decades based on a potent graft-versus-leukemia (GVL) effect expressed as a permanently active cellular immune therapy in the recipient, independent of chemotherapy-related cytotoxicity. As indicated in the Description section of this policy, allogeneic HCT may include use of myeloablative or reduced-intensity pretransplant conditioning regimens.

Data compiled in numerous review articles suggest that myeloablative allogeneic HCT has curative potential for CLL or SLL. Long-term disease control (33%-65% OS at 3-6 years) due to a low rate of late recurrences has been observed in all published series, regardless of donor source or conditioning regimen. However, high rates (24%-47%) of TRM discourage this approach in early or lower-risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The development of reduced-intensity conditioning (RIC) regimens has extended the use of allogeneic HCT to older or less fit patients who account for the larger proportion of this disease than younger patients, as outlined in several recent review articles. Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allogeneic HCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total-body irradiation. The majority of patients in these series were heavily pretreated, with a median of 3 to 5 courses of prior regimens. Among individual studies, 27%-57% of patients had chemotherapy-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18%-67%) received stem cells from a donor other than a human leukocyte antigen (HLA)–identical sibling. Reported NRM, associated primarily with graft-versus-host disease (GVHD) and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 to 5 years. Overall survival rates ranged from 48% to 70% at follow-up that ranged from 2 to 5 years. Similar results were reported for progression-free survival (PFS), 34% to 58% at 2- to 5-year follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HCT in patients (n=90; median age, 53 years; range, 27-65) with poor-risk CLL, defined as having one of the following: refractoriness or early relapse (ie, <12 months) after purine-analog therapy; relapse after autologous HCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated IgVh status and/or usage of the VH3-21 gene). With a median follow-up of 46 months, 4-year NRM, EFS, and OS were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

Autologous HCT

2015 systematic review of autologous HCT as front-line consolidation in CLL included a literature search through November 2014. Four RCTs in adult patients were included in the review. Outcomes included OS, PFS, EFS, and harms (adverse events, treatment-related mortality and secondary malignancies). Four studies met inclusion criteria, with 301 patients randomized to the autologous HCT arm and 299 to the
control arm using front-line therapy without HCT as consolidation. Autologous HCT did not result in a statistically significant improvement in OS (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.62 to 1.33) or in PFS (HR=0.70; 95% CI, 0.32 to 1.52). There was a statistically significant improvement in EFS favoring autologous HCT (HR=0.46; 95% CI, 0.26 to 0.83). There was not a higher rate of secondary malignancy or treatment-related mortality associated with autologous HCT.

A systematic review of autologous HCT for CLL or SLL included 9 studies (total n=361, 292 of which were transplanted) identified from a search of MEDLINE databases from 1966 to September 2006. Studies were included if they were full-publication English language reports of prospective randomized, nonrandomized, or single-arm design. The analysis suggested that autologous HCT may achieve significant clinical response rates (74%-100%) with relatively low treatment-related mortality (TRM) (0%–9%). However, molecular remissions are typically short-lived, with subsequent relapse. Overall survival (OS) ranged from 68% at 3-year follow-up to 58% at 6-year. Secondary myelodysplasia and myelodysplastic syndrome that may progress to frank acute myelogenous leukemia has been reported in 5% to 12% of patients in some studies of autologous HCT, which suggests caution in considering this approach, especially given the indolent nature of CLL or SLL. The authors of the review concluded that in the absence of randomized, comparative studies, it is uncertain whether autologous HCT is superior to conventional chemotherapy (or current chemo-immunotherapy) combinations as first-line consolidation treatment in CLL or SLL patients, regardless of disease risk, or as salvage therapy in those with relapsed disease.

The conclusions of the systematic review of autologous HCT outlined above are congruent with results of the Phase III European Intergroup randomized trial that compared autologous HCT (n=112) or postinduction observation (n=111) for consolidation in patients with CLL who were in complete remission (59% of total) or very good partial remission (27% of total) following fludarabine-containing induction therapy. Patient age ranged from 31 to 65 years, with Binet stage A progressive (14%), B (66%), and C (20%) disease. None were known to have 17p deletion; 45% were known to not carry 17p deletion, but that status was unknown in 54% of all patients. The primary outcome, median event-free survival (EFS), was 51 months (range, 40-62) in the autograft group, compared with 24 months (range, 17-32) in the observed group; the 5-year EFS was 42% and 24%, respectively (p<0.001). The relapse rate at 5-year follow-up was 54% in the autograft group versus 76% in the observational group (p<0.001); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range, 59-71) and 40 months (range, 25-56), respectively (p=0.002). Overall survival probability at 5-year follow-up was 86% (95% confidence interval [CI], 77% to 94%) in the autograft arm, versus 84% (95% CI, 75% to 93%) in the observation arm (p=0.77), with no evidence of a plateau in the curves. There was no significant difference in nonrelapse mortality (NRM) between groups, 4% in the autologous HCT group and 0% in the observation group (p=0.33). Myelodysplastic syndrome was observed at follow-up in 3 patients receiving an autograft and in 1 patient in the observational group.

In a subsequent report published in 2013, the authors of the European Intergroup randomized controlled trial (RCT) presented quality-of-life (QOL) findings from this trial. Two secondary analyses were performed to further investigate the impact of HCT and relapse on QOL. In the primary analysis, the authors demonstrate an adverse impact of HCT on QOL, which was largest at 4 months and continued throughout the first year after randomization. Further, a sustained adverse impact of relapse on QOL was observed, which worsened over time. Thus, despite better disease control by autologous HCT, the side effects turned the net effect toward inferior QOL in the first year and comparable QOL in the following 2 years after randomization.

Another RCT assessed the efficacy of autologous HCT in previously untreated CLL patients. A total of 244 patients (181 men) of median age 56 years (range, 31-66) had Binet stage B (n=185) or C (n=56) disease.
Among enrollees, 237 started planned therapy, 6 of whom discontinued. All 231 patients underwent induction chemotherapy; 103 (45%) entered complete remission and were randomly allocated to autologous HCT (n=52) or observation (n=53). The 3-year estimated OS rates were 98% (95% CI, 94% to 100%) in the observation arm, and 96% (95% CI, 90% to 100%) in the HCT arm (p=0.73). The estimated hazard ratio for death was 1.2 (95% CI, 0.3 to 3.8) in the HCT arm relative to the observation arm (p=0.82). During the 36 months after randomization, HCT was associated, on average, with an extra 9 months without clinical symptoms or blood signs of CLL progression (32±1 month) compared with observation (23±2 months).

The results of the GOELAMS LLC 98 randomized trial were published in final form in 2012. This trial aimed to compare 2 strategies in previously untreated high-risk CLL patients 60 years-old or younger. Arm A comprised conventional chemotherapy of 6 monthly courses of CHOP (vincristine, doxorubicin, and oral prednisone) followed by 6 additional CHOP courses every 3 months in patients who achieved a partial response (PR) or complete response (CR). Arm B consisted of 3 monthly CHOP courses; patients who achieved a very good partial response (VGPR) or CR received consolidation therapy consisting of high-dose cyclophosphamide plus total-body irradiation followed by autologous HCT; rituximab was not used in this study. Among 86 total patients, 39 and 43 were evaluable in arms A and B, respectively. The primary outcome was progression-free survival (PFS); on an intention-to-treat basis, the median PFS reached 22 months in arm A and 53 months in arm B at median follow-up of 77 months (p<0.001). Median OS time, however, was 104.7 months (95% CI, 99.9 to 109.5) in arm A and 107.4 months (95% CI, 58.2 to 156.6) in arm B, a nonsignificant difference. This trial shows that front-line high-dose therapy with autologous HCT prolongs PFS but does not significantly improve the duration of OS.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence

The evidence for allogeneic hematopoietic cell transplantation (allo-HCT) in individuals who have chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and markers of poor-risk disease includes single-arm prospective and registry-based studies and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data suggests that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The evidence for autologous hematopoietic cell transplantation in patients who have CLL/SLL includes randomized controlled trials (RCTs), systematic reviews, and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoinmunotherapy agents. Furthermore, evidence from the European Intergroup RCT suggests quality-of-life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach.
Clinical Guidelines

European Group for Blood and Marrow Transplantation

In June 2005, the European Group for Blood and Marrow Transplantation (EBMT) convened a consensus panel to identify situations in which allogeneic HCT is indicated for patients with CLL. Information for this evidence-based consensus was based on a MEDLINE search, meeting abstracts, and unpublished investigator-derived data. The panel considered 4 key issues:

- Does graft-versus-leukemia (GVL) activity in CLL exist?
- If yes, is it effective in high-risk CLL?
- What is the success rate of allogeneic HCT in CLL?
- Which prognostic risk level justifies allogeneic HCT?

The EBMT panel concluded that sound evidence exists that GVL activity is effective and represents the main contributor to durable disease control after allogeneic HCT, even in poor-risk patients. It further concluded that long-term disease-free survival and possibly cure may be achieved in 33%-67% of patients who undergo allogeneic HCT for poor-risk CLL. Although allogeneic HCT for CLL is a procedure with evidence-based efficacy for poor-risk CLL, evidence is not sufficient to identify a generally superior conditioning regimen. The optimum choice of conditioning regimens may vary: in the presence of older age, comorbidity and sensitive disease; RIC regimens might be appropriate, whereas myeloablative regimens might be preferable in younger patients with good performance status but poorly controlled disease. The EBMT statement further suggests that these cases be discussed with a transplant center as early as possible to avoid extensive cytotoxic pretreatment or disease transformation. Furthermore, because the optimum transplant strategy may vary according to the clinical situation, it should be defined whenever possible in approved prospective clinical protocols.

National Cancer Institute Working Group on CLL

In 1988 and 1996, a National Cancer Institute Working Group (NCI-WG) on CLL published guidelines for the design and conduct of clinical trials to facilitate comparisons between treatments and establish definitions that could be used in scientific studies on the biology of this disease. The U.S. Food and Drug Administration (FDA) also adopted these guidelines in their evaluation and approval of new agents. An updated version of the NCI-WG guidelines has been published that provides management recommendations based on new prognostic markers, diagnostic parameters, and treatment options. (28)

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network (NCCN) Guidelines (v2.2016) for non-Hodgkin lymphoma do not include autologous HCT as a therapeutic option in CLL or SLL. NCCN indicates that allogeneic HCT may be considered, preferably in a clinical trial, for patients

- Without del17p/TP53 mutation, with or without del 11q, for relapsed or refractory disease, if without significant comorbidities
- With del17p/TP53 mutation, as first line treatment if response to first-line therapy

VIII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

IX. References

2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose chemotherapy plus allogeneic stem cells to treat chronic lymphocytic leukemia or small lymphocytic lymphoma. TEC Assessments 2002, Volume 17, Tab 4.


